Sensitivity and specificity of linear array intraoperative ultrasound in glioblastoma surgery: a comparative study with high field intraoperative MRI and conventional sector array ultrasound

Jan Coburger, Angelika Scheuerle, Thomas Kapapa, Jens Engelke, Dietmar Rudolf Thal, Christian R. Wirtz, Ralph König

*Institute of Pathology – Laboratory of Neuropathology, Center for biomedical Research, University of Ulm, Ulm, Germany

Abstract

Introduction:

Linear array intraoperative ultrasound (lioUS) is an emerging technology for intracranial use. We evaluated sensitivity and specificity of lioUS to detect residual tumor in patients harboring a glioblastoma multiforme.

Methods:

After near total resection in 20 patients, residual tumor detection using lioUS, conventional intraoperative Ultrasound (cioUS) and Gd-DTPA enhanced intraoperative MRI (iMRI) were compared. Sensitivity and specificity were calculated based on 68 navigated biopsies. ROC curves and correlation with histopathological findings of each imaging modality were calculated. Additionally, results were evaluated in the subgroup of recurrent disease (n=23/68).

Results:

Sensitivity of lioUS (40%) was significantly higher compared to iMRI (19%) and cioUS (3%). Specificity of lioUS (23%) was significantly lower than in cioUS (60%) while there was no significant difference to iMRI (34%). All imaging modalities correlated significantly with histopathological findings. In the subgroup of recurrent disease sensitivity and specificity decreased in all modalities. However, cioUS showed significant lower values than iMRI and lioUS. In ROC curves, lioUS showed higher AUC in comparison to iMRI and cioUS. We found similar results in the subgroup of recurrent disease.

Conclusion:

Tumor detection using a lioUS is significantly superior to cioUS. Overall test performance in lioUS is comparable to results of iMRI. While the latter has a higher specificity and a significantly lower sensitivity in comparison to lioUS.

Keywords:

Linear array intraoperative ultrasound, intraoperative ultrasound, intraoperative MRI, glioblastoma multiforme, sensitivity, specificity, extend of resection

Introduction

There is growing evidence, that patients harboring a glioblastoma multiforme(GBM) only benefit from surgery if an extend of resection(EoR) above 95% is achieved. [19,10,14,25,20] These findings support the use of intraoperative imaging in GBM surgery. The only commercially available imaging methods to detect residual tumor during surgery are intraoperative ultrasound (ioUS) and intraoperative MRI (iMRI). For both methods a benefit to improve EoR and progression free survival (PFS) was shown. [24,26] For iMRI even class one evidence exists .

ioUS is the most commonly used intraoperative imaging modality. It is cost effective and has become well-established since its first introduction in neurosurgery by Chandler et al in 1982.[3] Transducer technology evolved over time with significant improvement of image quality and transducer size. For neurosurgical use, highest impact was made with the integration of the ultrasound device into a dedicated neuronavigation system (SonoWand®).[8] Thus a more precise resection control in glioma surgery and a detection of occurring brain shift was achieved. [30,21] Meanwhile, integration of any ultrasound probe in a neuronavigation system is possible and showed to be beneficial for the surgeon. [22,28] Yet, the major drawback of the conventional ultrasound technique is the increase of artifacts during surgery. Rygh et al report a significant drop of accuracy of ioUS during resection in high grade gliomas.[23] In direct comparison to iMRI, ioUS showed a significant lower detection rate of residual tumor while tumor depiction before resection was almost comparable.[7]

So far, for typical intracranial application sector or curved array transducers are used. Both use 4 to 8 MHz probes with a cone or trapezoid shape image. The advantage of these transducers is the relatively small probe design for intracranial use and the option of 3D image acquisition, as described by Bosinov et al. [1] Yet, the low frequency and the divergence of the ultrasound waves due to the cone or trapezoid shape ultrasound lead to a low resolution and high vulnerability to artifacts.

In contrary, linear array ultrasound transducers provide high resolution combined and little artifacts due to the linear phase array. Intraoperative tumor resection control using linear array intraoperative ultrasound (lioUS) increased gross total resection (GTR) rate significantly in breast cancer surgery. [13] The high potential for soft tissue differentiation using lioUS lead to a high accuracy in predicting final histopathological diagnosis in an experimental setting using breast tissue.[6] Recently small transducers applicable for intracranial use became available. Thus, the enormous potential of lioUS as a precise resection control is accessible. lioUS probes are available for the SonoWand® system and as separate transducers from most US manufactures.

At time of writing no comparison of accuracy for tumor detection of conventional ioUS (cioUS) and lioUS exists. All studies assessing EoR in GBMs are based on resection control using Gd-DTPA enhanced MRI. Therefore, we evaluate tumor detection of cioUS and lioUS against Gd-DTPA enhanced intraoperative high field MRI (iMRI). We used navigated ioUS and iMRI in order to avoid bias of brain shift or post-surgical changes. Thus, we compared three contemporary intraoperative imaging methods based on histopathological samples.

Differentiation between recurrent tumor and scar tissue in GBMs is challenging for MRI and ultrasound. Especially the latter technique is prone for artifacts in this entity due to the echogenity of scar tissue. Therefore we additionally evaluated accuracy of tumor detection in the subgroup of recurrent disease.

Methods:

Study design:

We used a prospective non randomized study design. We included patients harboring a contrast enhancing lesion eligible for a gross total removal after informed consent from August 2012 to

October 2013. Ethical approval was received by the local ethical committee with approval number 172/12.

Primary inclusion criteria were planed GTR and informed consent of the patient. Exclusion criteria were age under 18 or more than 75 years and final histopathological diagnosis different from a glioblastoma multiforme WHO°IV (GBM). Both primary and recurrent GBMs were included. We conducted a subgroup assessment for the latter group.

OR Setup

We performed all cases in a dedicated 1.5 Tesla iMRI (Magnetom Espree, Siemens Healthcare, Erlangen, Germany) environment with integrated data management and neuronavigation (Brainsuite®, Brainlab , Feldkirchen) running the Iplan 3.0 neuronavigation software (Brainlab, Feldkirchen, Germany).

Study protocol:

A typical microsurgical tumor resection was performed until the surgeon assumed a near total removal of lesion. Consequently, we assessed residual tumor first using cioUS than using lioUS. If, according to surgeon's judgment, conspicuous tissue was detected by either device, exact spatial location was marked in neuronavigation system. Then, we conducted an iMRI Scan (T1 & Gd-DTPA enhanced T1). Detection of residual tumor in iMRI was based on detection of Gd-DTPA enhancement alone. If additional imaging techniques like diffusion weighted imaging, T2, Flair or perfusion weighted imaging were performed at surgeon discretion, data were not included in the study. Suspicious tissue, detected in iMRI was marked and cross referenced with findings in cioUS and lioUS and the other way around. Navigated biopsies were taken from these respective sites and negative "control" areas.

Ultrasound

We performed intraoperative ultrasound with an iU22 xMatrix Ultrasound system (Philips, Amsterdam, Netherlands).

For conventional intraoperative ultrasound (cioUS) we used a X7-2 xMatrix array 3D probe (Philips, Amsterdam, Netherlands). The transducer is a 3D matrix array probe with 2500 elements using a 7 to 2 MHz extended operating frequency range.

For linear array intraoperative ultrasound lioUS, we applied a L15-7io compact hockey stick shaped linear array transducer (11x31mm, 128 elements) with an extended frequency range of 15 to 7 MHz.

Both ultrasound probes were registered to the neuronavigation system as described before[5] in order to define the exact spatial location of residual tumor detected by the ultrasound system.

Intraoperative MRI

Intraoperatively we routinely performed a T1 MPRAGE with and without Gd-DTPA and an axial T2 and Flair sequence. Timing of iMRI was as described in the study protocol. Additional iMRI scans were performed at surgeon's discretions. Only results of first iMRI were evaluated as part of the study. We evaluated only the residual contrast enhancement of iMRI, non-enhancing tumor, like FLAIR changes etc., was not evaluated in this study.

Histopathological assessment

Samples from navigated biopsies for histopathological assessment were categorized by the neurosurgeon according to the imaging results and forwarded to pathology as separate samples. The neuropathologists were blinded to the clinical categorization of the samples. Two neuropathologists observed the samples separately. In case of disagreement, the neuropathologists discussed the sample and agreed into a consensus diagnosis.

All samples were fixed in 10% phosphate-buffered formalin and embedded in paraffin. GBMs were classified neuropathologically according to the World Health Organization (WHO) central nervous tissue tumor classification.[16] For this purpose paraffin sections were stained with

hematoxylin&eosin (H&E). Immunohistochemistry for glioblastomas was carried out with antibodies raised against glial fibrillary acidic protein (GFAP; polyclonal rabbit, 1/1000, DAKO, Glostrup, Denmark), microtubule-associated protein MAP2 (HM-2, 1/500, heat pretreatment, Sigma-Aldrich, St. Louis, MO, USA), mutant isocitrate dehydrogenase 1 (mIDH1; Dianova, Hamburg, Germany)and the ki67-epitope (MIB1, 1/100, heat pretreatment, DAKO, Glostrup, Denmark).

Pathologically samples were classified as “solid tumor” if they matched all WHO criteria for a °IV lesion. In contrary, we defined “no solid tumor” as tissue not matching with the above cited WHO criteria. Thus, “no solid tumor” in a glioblastoma might include infiltration zone of tumor as well as tissue most likely free of tumor cells.

Statistical assessment

We calculated sensitivity and specificity according to the common criteria. We tested for a statistical different distribution to detect tumor positive areas (sensitivity) and tumor negative areas (specificity) using McNemar´s test. We used Spearsman´s rho to test for significant correlations between tested imaging methods (iMRI, cioUS, lioUS) and histopathological findings. Receiver operator characteristic (ROC) curves and area und the curve (AUC) were calculated. AUC were interpreted as described by Hanley et al[9]

All statistical tests were performed with SPSS 20.0 (Lead Technologies, INC, Charlotte, USA).

Results:

Patient’s characteristics:

We prospectively enrolled 20 patients. 68 histopathological samples were harvested via navigated biopsies during these surgeries. Patient´s characteristics are summarized in table 1. Due to the rare occurrence of infratentorial GBMs and the rare indication to perform surgery in a deep-seated GBM only typical supratentorial lobar lesions were treated. We did not exclude lesions by location according to the study protocol.

Overall test results:

Calculation of sensitivity and specificity

The distribution of solid tumor detection is distinctly different in all 3 imaging modalities (table 2), thus leading to heterogeneous test results for sensitivity and specificity. (table 3). lioUS shows highest *sensitivity* (true positive values when tumor was present) with 76%. iMRI showed a sensitivity of 55% and cioUS of only 24%. The calculation of *specificity* (true negative results when no tumor was present) showed contrary results; cioUS showed highest specificity with 96%. iMRI showed 74% while lioUS reached 58%.

Sensitivity (tumor was present) was significantly different between lioUS and cioUS ($p<0.001$) and between lioUS and iMRI ($p<0.021$). Also, between cioUS and iMRI was a significant difference in sensitivity ($p<0.001$).
Specificity (no tumor was present) was significantly different between lioUS and cioUS ($p<0.016$). No statistical difference was seen between specificity of lioUS and iMRI. No significant difference was found between iMRI and cioUS, as well.

Receiver Operating Characteristic

ROC curves are shown in figure 1. AUC was highest in lioUS (0.667) compared to iMRI (0.644) and cioUS (0.596). Both iMRI and lioUS show a poor accuracy in this setup (AUC 0.6 -0.7). cioUS failed to discriminate “solid tumor” from “no tumor” (AUC <0.6).

Only for lioUS a significant difference ($p<0.034$) from 0.5(no discrimination) could be proven, while iMRI showed a tendency for a significant difference ($p<0.067$) (Table 5).

Subgroup of recurrent disease

Calculation of sensitivity and specificity

In the subgroup of recurrent disease we found a drop of sensitivity in cioUS to 21.05%, while iMRI and lioUS showed a slight increase of sensitivity to 63.16% and 84.21% respectively. (Table 4) The difference in sensitivity to cioUS was significant in iMRI ($p<0.021$) and lioUS ($p<0.002$). Statistically no difference in sensitivity was seen between iMRI and lioUS.
Specificity was significantly higher ($p<0.31$) in cioUS (100%) in comparison to lioUS (75%) and iMRI (75%).

Receiver Operating Characteristic

ROC curves are shown in figure 2. AUC was highest in lioUS (0.796) compared to iMRI (0.691) and cioUS (0.605). According to Hanley et al; lioUS reached a fair accuracy (0.7-0.8), iMRI and cioUS had a poor accuracy (0.6 – 0.7). Yet, none of the methods showed a significant difference from 0.5. (Table 6)

Discussion

Linear array intraoperative ultrasound (lioUS) is an emerging technology in neurosurgery. Excellent image quality and real time tissue assessment using the technique was shown in peripheral nerve surgery. [11,12] Bozinov et al described the application for spinal cord surgery. [2] Moiyadi et al described use of a 12Mhz transducer as part of SonoWand® system in 10 cases as part of a larger series.[17] Yet, at time of writing intracranial use of lioUS has not been evaluated in detail.

Aim of the prospective study was to compare sensitivity and specificity for tumor detection of lioUS, conventional ioUS (cioUS) and intraoperative MRI (iMRI). We used two state of the art ultrasound transducers. For lioUS we applied a 7 to 15 MHz hockey stick shaped transducer. In comparison to other linear array transducers this probe combines a high resolution (0.5 – 1mm) with a penetration depth comparable to a conventional low frequency ultrasound.[18] For cioUS a high-end sector array transducer was used. The innovative intracranial application and the high resolution of this transducer was described for pediatric and adult patients.[29,1]

In our series both ultrasound modalities were registered to the neuronavigation system. After ultrasound examintation an intraoperative MRI was performed before harvesting of histopathological samples. Thus, we controlled for occurring brain shift and enabled for a direct comparison of tumor depiction in each ultrasound method together with the Gd-DTPA enhanced MRI. Tumor detection was cross validated between all three methods in order to compensate for a bias due to sequential design of application.

We found a significant higher sensitivity for solid tumor detection using lioUS in comparison to cioUS and iMRI. Yet, specificity was lower using the linear array transducer. However, using receiver operator characteristics(ROC) which is a very strong test to evaluate diagnostic instruments, lioUS was the only imaging modality differentiating significantly from 0.5(no discrimination line). Apart from this, iMRI and lioUS had very similar accuracies as demonstrated by the area under the curve (AUC). Only cioUS failed to discriminate between residual solid tumor and no tumor in our study. Concerning cioUS our results are comparable to the findings by Rygh et al.. The authors assessed sensitivity and specificity before, during and after resection.[23] The results of our study are comparable to their findings “after resection” since study protocol implicated a near total resection before application of ioUS. Rygh et al found a sensitivity of 26% and a specificity of 88% for cioUS which is similar to our data. Gerganov et al found a high rate of false positive and false negative results using cioUS in comparison to iMRI.[7] The authors do not provide exact calculation for

sensitivity and specificity. For cioUS, we did only have one case with a false positive finding while the device was false negative in the majority of cases. Except for the above mentioned study, no comparative data exist for high field iMRI and cioUS. Few data exist on actual histopathological correlation of imaging findings of Gd-DTPA enhanced iMRI; Kubben et al found a sensitivity of 49% and a specificity of 100%. While Sensitivity is comparable to our data, specificity is much higher. [15] This might be because the authors defined tumor as tissue matching with WHO°III or °IV criteria. In our series "solid tumor" was defined as tissue expressing all features of a °IV lesion only. Our own data evaluating iMRI and 5-Aminolevulinic acid shows a slightly lower sensitivity and a similar specificity as in the actual data. [4] At time of writing no data exits concerning accuracy of lioUS in glioma surgery.

We performed a subgroup analysis for residual tumor. This entity is challenging for ioUS evaluation due to high echogenity of scar tissue which can easily be misinterpreted as tumor. As Solheim et al evaluated, there is a drop of image quality and an increase of underestimation of residual tumor in non-primary lesions using cioUS. Even though results were not significant, the data suggested a correlation of image quality and previous radiation and/or recurrent surgery. [27] Our data shows that lioUS seems to overcome this issue in ioUS. We found a significant higher sensitivity for residual tumor in comparison to cioUS and a fair accuracy of lioUS in AUC. For recurrent disease no significant difference of the test results was found between iMRI and lioUS.

The actual comparison shows a superiority of lioUS in comparison to cioUS. The data even suggests a higher detection rate of residual tumor in comparison to iMRI. Test performance measures using iMRI was based on Gd-DTPA enhancement alone. No advanced imaging sequences (Diffusion, Perfusion, Flair etc.) were evaluated. Therefore the actual accuracy of iMRI might be underestimated.

Additionally, we used a rigid study protocol with cross validation of conspicuous areas using all imaging modalities. Thus, the clinical impact on EoR of lioUS might be lower than the actual test results suggest. Using iMRI residual contrast enhancement is hard to miss.

Detecting a small echogenic area using a small high definition lioUS in a large resection cavity is more challenging. Additionally, we performed all ultrasound procedures navigated. Especially the lioUS should only be used integrated in a neuronavigation system. From our point of view the potential of the high resolution of the transducer cannot be used appropriately otherwise. Field of view of the device is small and orientation while using intracavital ultrasound can be challenging.

Our test results for accuracy (sensitivity, specificity, ROC calculations) refer to residual tumor detection. cioUS failed to distinguish between tumor and no tumor in this setup. Yet, using cioUS for orientation and tumor detection before resection is still highly beneficial for the surgeon. Especially the wide-angle field of view and the higher penetration depth allows for a valuable detection of adjacent anatomical structures (e.g. ventricle, falx, skull base etc.) and a good brain shift control.

Our data suggest that tumor detection using lioUS and using iMRI is "different" even though accuracy values are similar. lioUS shows a slight "over-detection" while iMRI in contrary has an "under-detection" of relevant solid tumor tissue. lioUS shows a significantly superior sensitivity for solid tumor detection compared to iMRI. iMRI in contrary shows a higher specificity and a better overview of the resection cavity and adjacent structures. Hence, a supplementary use of lioUS with iMRI might be of additional benefit for EoR. Further studies are needed in this regard.

According to our results, lioUS is an ideal tool for centers, which do not host an iMRI. The lioUS shows an accuracy comparable to iMRI and is easily available to any center without substantial investment and protracted planning. lioUS transducers integrated in a neuronavigation system are a very cost effective solution to improve residual tumor detection during surgery of GBMs. Further data is needed assessing the impact on EoR using lioUS transducers. Yet, our data highly suggest a superiority in comparison to cioUS.

Conclusion:

Tumor detection using a lioUS is significantly superior to cioUS. Overall test performance in lioUS is comparable to results of iMRI. While the latter has a higher specificity and a significantly lower sensitivity in comparison to lioUS.

Disclosure Statement

DRT received consultancies from Simon-Kucher and Partners (Germany), Covance Laboratories (UK) and GE-Healthcare (UK), received a speaker honorarium from GE-Healthcare (UK) and collaborated with Novartis Pharma Basel (Switzerland).

1. Bozinov O, Burkhardt JK (2012) Intra-operative computed-tomography-like real-time three-dimensional ultrasound in neurosurgery. World Neurosurg 78 (1-2):5-7. doi:10.1016/j.wneu.2012.05.025
2. Bozinov O, Burkhardt JK, Woernle CM, Hagel V, Ulrich NH, Krayenbuhl N, Bertalanffy H (2012) Intra-operative high frequency ultrasound improves surgery of intramedullary cavernous malformations. Neurosurg Rev 35 (2):269-275; discussion 275. doi:10.1007/s10143-011-0364-z
3. Chandler WF, Knake JE, McGillicuddy JE, Lillehei KO, Silver TM (1982) Intraoperative use of real-time ultrasonography in neurosurgery. J Neurosurg 57 (2):157-163. doi:10.3171/jns.1982.57.2.0157
4. Coburger J, Engelke J, Scheuerle A, Thal DR, Hlavac M, Wirtz CR, König R (2014) Tumor detection with 5-aminolevulinic acid fluorescence and Gd-DTPA–enhanced intraoperative MRI at the border of contrast-enhancing lesions: a prospective study based on histopathological assessment. Neurosurg Focus 36 (2):E3. doi:doi:10.3171/2013.11.FOCUS13463
5. Coburger J, König RW, Scheuerle A, Engelke J, Hlavac M, Thal DR, Wirtz CR (2014) Navigated high frequency ultrasound: Description of technique and first clinical comparison with conventional intracranial ultrasound. World Neurosurg
6. Doyle TE, Factor RE, Ellefson CL, Sorensen KM, Ambrose BJ, Goodrich JB, Hart VP, Jensen SC, Patel H, Neumayer LA (2011) High-frequency ultrasound for intraoperative margin assessments in breast conservation surgery: a feasibility study. BMC Cancer 11:444
7. Gerganov VM, Samii A, Akbarian A, Stieglitz L, Samii M, Fahlbusch R (2009) Reliability of intraoperative high-resolution 2D ultrasound as an alternative to high-field strength MR imaging for tumor resection control: a prospective comparative study. Journal of Neurosurgery 111 (3):512-519
8. Gronningsaeter A, Kleven A, Ommedal S, Aarseth TE, Lie T, Lindseth F, Lango T, Unsgard G (2000) SonoWand, an ultrasound-based neuronavigation system. Neurosurgery 47 (6):1373-1379; discussion 1379-1380
9. Hanley JA, McNeil BJ (1982) The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 143 (1):29-36. doi:doi:10.1148/radiology.143.1.7063747
10. Hess KR (1999) Extent of resection as a prognostic variable in the treatment of gliomas. J Neurooncol 42 (3):227-231
11. Koenig RW, Pedro MT, Heinen CP, Schmidt T, Richter HP, Antoniadis G, Kretschmer T (2009) High-resolution ultrasonography in evaluating peripheral nerve entrapment and trauma. Neurosurg Focus 26 (2):E13

12. Koenig RW, Schmidt TE, Heinen CP, Wirtz CR, Kretschmer T, Antoniadis G, Pedro MT (2011) Intraoperative high-resolution ultrasound: a new technique in the management of peripheral nerve disorders. Journal of Neurosurgery 114 (2):514-521
13. Krekel NM, Zonderhuis BM, Schreurs HW, Cardozo AM, Rijna H, van der Veen H, Muller S, Poortman P, de Widt L, de Roos WK, Bosch AM, Taets van Amerongen AH, Bergers E, van der Linden MH, de Lange de Klerk ES, Winters HA, Meijer S, van den Tol PM (2011) Ultrasound-guided breast-sparing surgery to improve cosmetic outcomes and quality of life. A prospective multicentre randomised controlled clinical trial comparing ultrasound-guided surgery to traditional palpation-guided surgery (COBALT trial). BMC surgery 11:8. doi:10.1186/1471-2482-11-8
14. Kreth FW, Berlis A, Spiropoulou V, Faist M, Scheremet R, Rossner R, Volk B, Ostertag CB (1999) The role of tumor resection in the treatment of glioblastoma multiforme in adults. Cancer 86 (10):2117-2123
15. Kubben PL, Wesseling P, Lammens M, Schijns OE, Ter Laak-Poort MP, van Overbeeke JJ, van Santbrink H (2012) Correlation between contrast enhancement on intraoperative magnetic resonance imaging and histopathology in glioblastoma. Surgical neurology international 3:158
16. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P (2007) The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol 114 (2):97-109
17. Moiyadi A, Shetty P, Mahajan A, Udare A, Sridhar E (2013) Usefulness of three-dimensional navigable intraoperative ultrasound in resection of brain tumors with a special emphasis on malignant gliomas. Acta Neurochirurgica 155 (12):2217-2225. doi:10.1007/s00701-013-1881-z
18. Moran CM, Pye SD, Ellis W, Janeczko A, Morris KD, McNeilly AS, Fraser HM (2011) A comparison of the imaging performance of high resolution ultrasound scanners for preclinical imaging. Ultrasound in medicine & biology 37 (3):493-501. doi:10.1016/j.ultrasmedbio.2010.11.010
19. Oszvald Á, Güresir E, Setzer M, Vatter H, Senft C, Seifert V, Franz K (2012) Glioblastoma therapy in the elderly and the importance of the extent of resection regardless of age. Journal of Neurosurgery 116 (2):357-364. doi:doi:10.3171/2011.8.JNS102114
20. Pichlmeier U, Bink A, Schackert G, Stummer W (2008) Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. Neuro-oncology 10 (6):1025-1034
21. Rasmussen IA, Jr., Lindseth F, Rygh OM, Berntsen EM, Selbekk T, Xu J, Nagelhus Hernes TA, Harg E, Haberg A, Unsgaard G (2007) Functional neuronavigation combined with intra-operative 3D ultrasound: initial experiences during surgical resections close to eloquent brain areas and future directions in automatic brain shift compensation of preoperative data. Acta neurochirurgica 149 (4):365-378
22. Renovanz M, Hickmann AK, Henkel C, Nadji-Ohl M, Hopf NJ (2014) Navigated versus Non-Navigated Intraoperative Ultrasound: Is There Any Impact on the Extent of Resection of High-Grade Gliomas? A Retrospective Clinical Analysis. J Neurol Surg A Cent Eur Neurosurg. doi:10.1055/s-0033-1356486
23. Rygh OM, Selbekk T, Torp SH, Lydersen S, Hernes TA, Unsgaard G (2008) Comparison of navigated 3D ultrasound findings with histopathology in subsequent phases of glioblastoma resection. Acta Neurochir (Wien) 150 (10):1033-1041; discussion 1042. doi:10.1007/s00701-008-0017-3
24. Saether CA, Torsteinsen M, Torp SH, Sundstrom S, Unsgard G, Solheim O (2012) Did survival improve after the implementation of intraoperative neuronavigation and 3D ultrasound in glioblastoma surgery? A retrospective analysis of 192 primary operations. J Neurol Surg A Cent Eur Neurosurg 73 (2):73-78
25. Sanai N, Berger MS (2008) Glioma extent of resection and its impact on patient outcome. Neurosurgery 62 (4):753-764; discussion 264-756. doi:10.1227/01.neu.0000318159.21731.cf

26. Senft C, Bink A, Franz K, Vatter H, Gasser T, Seifert V (2011) Intraoperative MRI guidance and extent of resection in glioma surgery: a randomised, controlled trial. The Lancet Oncology 12 (11):997-1003. doi:10.1016/s1470-2045(11)70196-6
27. Solheim O, Selbekk T, Jakola A, Unsgård G (2010) Ultrasound-guided operations in unselected high-grade gliomas—overall results, impact of image quality and patient selection. Acta Neurochirurgica 152 (11):1873-1886. doi:10.1007/s00701-010-0731-5
28. Tirakotai W, Miller D, Heinze S, Benes L, Bertalanffy H, Sure U (2006) A novel platform for image-guided ultrasound. Neurosurgery 58 (4):710-718; discussion 710-718. doi:10.1227/01.neu.0000204454.52414.7a
29. Ulrich NH, Burkhardt JK, Serra C, Bernays RL, Bozinov O (2012) Resection of pediatric intracerebral tumors with the aid of intraoperative real-time 3-D ultrasound. Childs Nerv Syst 28 (1):101-109. doi:10.1007/s00381-011-1571-1
30. Unsgard G, Solheim O, Lindseth F, Selbekk T (2011) Intra-operative imaging with 3D ultrasound in neurosurgery. Acta Neurochir Suppl 109:181-186